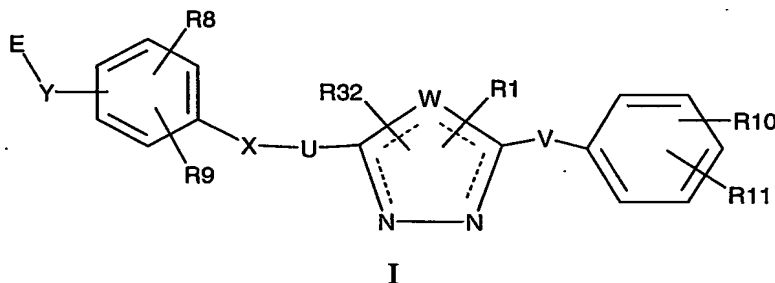


- 136 -

CLAIMS

What is claimed is:

- 5 1. A compound of the Formula I:



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

- 10 (a) R1 is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, C₁-C₈ heteroalkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and, wherein C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each
- 15 optionally substituted with from one to three substituents independently selected from R1';
- (b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR₁₂, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀₋₄-alkyl, heteroaryl, heterocycloalkyl, C(O)R₁₃, COOR₁₄, OC(O)R₁₅, OS(O)₂R₁₆, N(R₁₇)₂, NR₁₈C(O)R₁₉, NR₂₀SO₂R₂₁, SR₂₂, S(O)R₂₃, S(O)₂R₂₄, and S(O)₂N(R₂₅)₂; R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄ and R₂₅ are each independently selected from the group
- 20 consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (c) V is selected from the group consisting of C₀-C₈ alkyl and C₁₋₆-heteroalkyl;
- 25

- 137 -

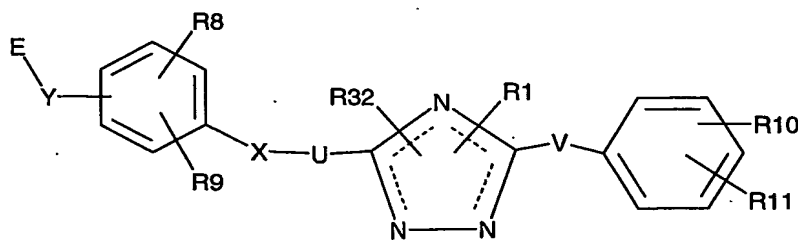
- (d) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;
- (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R₃₀;
- (f) W is N, O or S;
- (g) Y is selected from the group consisting of C, O, S, NH, and a single bond;
- (h) E is C(R₃)(R₄)A or A and wherein
- (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkynitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R⁷;
- (ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;
- (iii) R₃ is selected from the group consisting of hydrogen, C₁-C₅ alkyl, and C₁-C₅ alkoxy; and
- (iv) R₄ is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R₃ and R₄ are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R₂₆;
- (i) R₈ is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;
- (j) R₉ is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR₂₉, and wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R₂₇; R₂₉ is selected from the group consisting of hydrogen and C₁-C₄ alkyl;

- 138 -

- (k) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkylenyl, C₁-C₆ alkyl-COOR₁₂'', C₀-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, aryloxy, C(O)R₁₃', COOR₁₄', OC(O)R₁₅', OS(O)₂R₁₆', N(R₁₇')₂, NR₁₈'C(O)R₁₉', NR₂₀'SO₂R₂₁', SR₂₂', S(O)R₂₃', S(O)₂R₂₄', and S(O)₂N(R₂₅')₂; and wherein aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three independently selected from R₂₈; and wherein R₁₀ and R₁₁ optionally combine to form a 5 to 6 membered fused bicyclic ring with the phenyl to which they are bound;
- (l) R₁₂', R₁₂'', R₁₃', R₁₄', R₁₅', R₁₆', R₁₇', R₁₈', R₁₉', R₂₀', R₂₁', R₂₂', R₂₃', R₂₄', and R₂₅' are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (m) R₃₀ is selected from the group consisting of C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and wherein C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents each independently selected from R₃₁;
- (n) R₃₂ is selected from the group consisting of a bond, hydrogen, halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, and C₁-C₆ alkyloxo; and
- (o) ---- is optionally a bond to form a double bond at the indicated position.

2. A compound as claimed by Claim 1, wherein the compound is of the Formula Ia:

- 139 -



II

and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

- 5 (a) R1 is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and, wherein C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from
 10 one to three substituents independently selected from R1';
- (b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR₁₂, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀₋₄-alkyl, heteroaryl,
 15 heterocycloalkyl, C(O)R₁₃, COOR₁₄, OC(O)R₁₅, OS(O)₂R₁₆, N(R₁₇)₂, NR₁₈C(O)R₁₉, NR₂₀SO₂R₂₁, SR₂₂, S(O)R₂₃, S(O)₂R₂₄, and S(O)₂N(R₂₅)₂; R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄ and R₂₅ are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- 20 (c) V is selected from the group consisting of C₀-C₈ alkyl and C₁₋₄-heteroalkyl;
- (d) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;
- 25 (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R₃₀;

- 140 -

- (f) Y is selected from the group consisting of C, NH, and a single bond;
- (g) E is C(R3)(R4)A or A and wherein
- (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkynitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R⁷;
 - (ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;
 - (iii) R₃ is selected from the group consisting of hydrogen, C₁-C₅ alkyl, and C₁-C₅ alkoxy; and
 - (iv) R₄ is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R₃ and R₄ are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R₂₆;
 - (h) R₈ is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;
 - (i) R₉ is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR₂₉, and wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R₂₇; R₂₉ is selected from the group consisting of hydrogen and C₁-C₄ alkyl;
 - (j) R₁₀, R₁₁ are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkylenyl, C₁-C₆ alkyl-COOR₁₂'', C₀-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, aryloxy, C(O)R₁₃', COOR₁₄', OC(O)R₁₅', OS(O)₂R₁₆', N(R₁₇')₂,

- 141 -

NR18'C(O)R19', NR20'SO₂R21', SR22', S(O)R23', S(O)₂R24', and S(O)₂N(R25')₂; and wherein aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C3-C6 cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three independently selected from R28; and wherein R10 and R11 optionally combine to form a 5 to 6

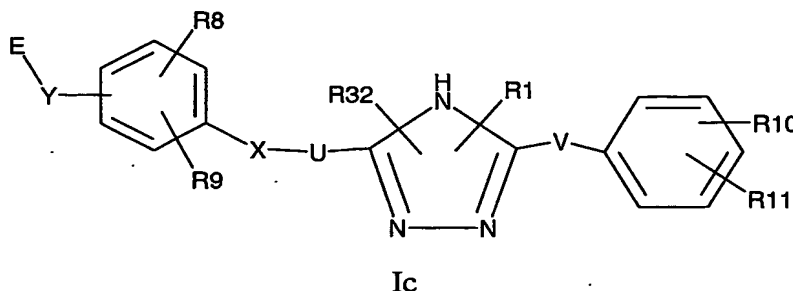
(k) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;

(l) R30 is selected from the group consisting of C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C3-C6 cycloalkylaryl-C₀₋₂-alkyl, and wherein C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C3-C6 cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;

(m) R32 is selected from the group consisting of a bond, hydrogen, halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, and C₁-C₆ alkyloxy; and

(n) ---- is optionally a bond to form a double bond at the indicated position.

3. A compound as claimed by Claim 1 wherein the compound is of the Formula Ic:



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates

thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, C₁-C₈ heteroalkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl,

- 142 -

heteroaryl-C₀₋₄-alkyl, and C3-C6 cycloalkylaryl-C₀₋₂-alkyl, and, wherein C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C3-C6 cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents independently selected from R^{1'};

(b) R^{1'}, R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR₁₂, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀₋₄-alkyl, heteroaryl, heterocycloalkyl, C(O)R₁₃, COOR₁₄, OC(O)R₁₅, OS(O)₂R₁₆, N(R₁₇)₂, NR₁₈C(O)R₁₉, NR₂₀SO₂R₂₁, SR₂₂, S(O)R₂₃, S(O)₂R₂₄, and S(O)₂N(R₂₅)₂; R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄ and R₂₅ are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;

(c) V is selected from the group consisting of C₀-C₈ alkyl and C₁₋₄-heteroalkyl;

(d) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;

(e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is substituted with from one to four substituents each independently selected from R₃₀;

(f) Y is selected from the group consisting of C, O, S, NH, and a single bond;

(g) E is C(R₃)(R₄)A or A and wherein

(i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkynitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R⁷;

(ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;

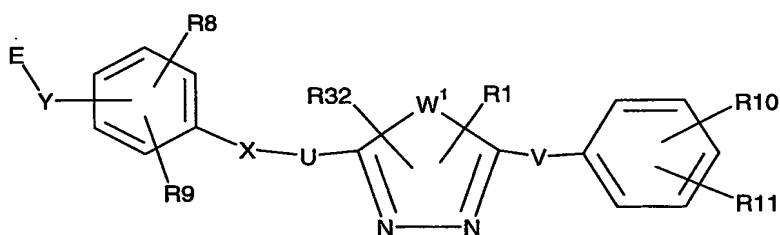
- 143 -

- (iii) R3 is selected from the group consisting of hydrogen, C₁-C₅ alkyl, and C₁-C₅ alkoxy; and
- (iv) R4 is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R3 and R4 are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R26;
- (h) R8 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;
- (i) R9 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR29, and wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C₁-C₄ alkyl;
- (j) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkylenyl, C₁-C₆ alkyl-COOR12'', C₀-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', OS(O)₂R16', N(R17')₂, NR18'C(O)R19', NR20'SO₂R21', SR22', S(O)R23', S(O)₂R24', and S(O)₂N(R25')₂; and wherein aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three independently selected from R28; and wherein R10 and R11 optionally combine to form a 5 to 6 membered fused bicyclic ring with the phenyl to which they are bound;
- (k) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;

- 144 -

- (l) R30 is selected from the group consisting of C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C3-C6 cycloalkylaryl-C₀₋₂-alkyl, and wherein C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C3-C6 cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;
- (m) R32 is selected from the group consisting of a bond, hydrogen, halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, and C₁-C₆ alkyloxo; and
- (n) ---- is optionally a bond to form a double bond at the indicated position.

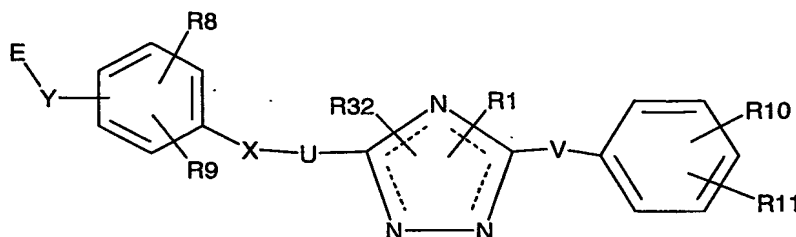
4. A compound as claimed by Claim 1, wherein the compound is of the Formula Ib:



wherein W¹ is S or O.

5. A compound of Claim 5 wherein W¹ is S.
6. A compound of Claim 5 wherein W¹ is O.
7. A compound as claimed by any one of Claims 4, 5, or 6 wherein when Y is O, then U is C₁-C₄ aliphatic linker wherein one carbon of the C₁-C₄alkyl is replaced with O and wherein the aliphatic linker is optionally substituted with from one to four substituents each independently selected from R30.
8. A compound as claimed by any one of Claims 1, 2, 3, or 7 wherein the compound is of the Formula III:

- 145 -



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

- (a) R1 is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, C₁-C₈ heteroalkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and, wherein C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents independently selected from R1';
- (b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR₁₂, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀₋₄-alkyl, heteroaryl, heterocycloalkyl, C(O)R₁₃, COOR₁₄, OC(O)R₁₅, OS(O)₂R₁₆, N(R₁₇)₂, NR₁₈C(O)R₁₉, NR₂₀SO₂R₂₁, SR₂₂, S(O)R₂₃, S(O)₂R₂₄, and S(O)₂N(R₂₅)₂; R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄ and R₂₅ are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (c) V is selected from the group consisting of C₀-C₈ alkyl and C₁₋₄-heteroalkyl;
- (d) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;
- (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R₃₀;

- 146 -

- (f) Y is selected from the group consisting of C, O, S, NH, and a single bond;
- (g) E is C(R3)(R4)A; wherein
- (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R⁷;
- (ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;
- (iii) R3 is selected from the group consisting of C₁-C₅ alkyl, and C₁-C₅ alkoxy; and
- (iv) R4 is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R3 and R4 are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R₂₆;
- with the proviso that when Y is O then R4 is selected from the group consisting of C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R3 and R4 are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, cycloalkyl and aryl-alkyl are each optionally substituted with one to three each independently selected from R₂₆;
- (h) R8 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;
- (i) R9 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR₂₉, and wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R₂₇; R₂₉ is selected from the group consisting of hydrogen and C₁-C₄ alkyl;

- 147 -

- (j) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkylenyl, C₁-C₆ alkyl-COOR₁₂'', C₀-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, aryloxy, C(O)R₁₃', COOR₁₄', OC(O)R₁₅', OS(O)₂R₁₆', N(R₁₇')₂, NR₁₈'C(O)R₁₉', NR₂₀'SO₂R₂₁', SR₂₂', S(O)R₂₃', S(O)₂R₂₄', and S(O)₂N(R₂₅')₂; and wherein aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three independently selected from R₂₈; and wherein R10 and R11 optionally combine to form a 5 to 6 membered fused bicyclic ring with the phenyl to which they are bound;
- (k) R₁₂', R₁₂'', R₁₃', R₁₄', R₁₅', R₁₆', R₁₇', R₁₈', R₁₉', R₂₀', R₂₁', R₂₂', R₂₃', R₂₄', and R₂₅' are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (l) R₃₀ is selected from the group consisting of C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and wherein C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents each independently selected from R₃₁;
- (m) R₃₂ is selected from the group consisting of a bond, hydrogen, halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, and C₁-C₆ alkyloxy; and
- (n) ---- is optionally a bond to form a double bond at the indicated position.
9. A compound as claimed by any one of Claims 1 through 8 wherein X is O.
10. A compound as claimed by any one of Claims 1 through 8 wherein X is S.

- 148 -

11. A compound as claimed by any one of Claims 1 through 10 wherein Y is
O.

12. A compound as claimed by any one of Claims 1 through 10 wherein Y is
5 C.

13. A compound as claimed by any one of Claims 1 through 10 wherein Y is
S.

14. A compound as claimed by any one of Claims 1 through 13 wherein two
of "----" in the five membered ring are each a bond to form double bonds at the
10 designated locations.

15. A compound as claimed by any one of Claims 1 through 14 wherein E is
C(R3)(R4)A.

16. A compound as claimed by any one of Claims 1 through 15 wherein A is
15 COOH.

17. A compound as claimed by any one of Claims 1 through 16 wherein R10
is haloalkyl.
20

18. A compound as claimed by Claim 17 wherein R10 is CF₃.

19. A compound as claimed by any one of Claims 1 through 16 wherein R10
is haloalkyloxy.
25

20. A compound as claimed by any one of Claims 1 through 16 wherein R10
and R11 are each independently selected from the group consisting of hydrogen, halo,
oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR₁₂'', C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆
haloalkyloxy.

21. A compound as claimed by any one of Claims 1 through 16 wherein R10 and
30 R11 are each independently selected from the group consisting of C₁-C₂ alkyl.

- 149 -

22. A compound as claimed by any one of Claims 1 through 16 wherein R10 is selected from the group consisting of C₃-C₇ cycloalkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and aryloxy.

5 23. A compound as claimed by any one of Claims 1 through 22 wherein R1 is optionally substituted C₂-C₃ arylalkyl.

10 24. A compound as claimed by any one of Claims 1 through 23, wherein R₈ and R₉ are each independently selected from the group consisting of hydrogen and C₁-C₃ alkyl.

15 25. A compound as claimed by any one of Claims 1 through 22 and 24 wherein R₁, V, R₃, and R₄ are each independently selected from the group consisting of C₁-C₂ alkyl.

26. A compound as claimed by any one of Claims 1 through Claim 22 and 24 wherein R₁, R₃, and R₄ are each independently selected from the group consisting of hydrogen and C₁-C₂ alkyl.

20 27. A compound as claimed by any one of Claims 1 through 24 or Claim 26 wherein V is a bond.

25 28. A compound as claimed by any one of Claims 1 through 24 wherein V is selected from the group consisting of C₀-C₁ alkyl.

29. A compound as claimed by any one of Claims 1 through 28 wherein U is C₁-C₃ alkyl.

30 30. A compound as claimed by any one of Claims 1 through 29 wherein U is saturated.

- 150 -

31. A compound as claimed by any one of Claims 1 through 22 or 24 through 30 wherein R1 is C1-C6 heteroalkyl.

32. A compound as claimed by any one of Claims 1 through 31 wherein one carbon of the aliphatic linker is replaced with an O.

33. A compound as claimed by any one of Claims 1 through 31 wherein U is an aliphatic linker having one carbon replaced by N.

34. A compound as claimed by any one of Claims 1 through 31 wherein U is an aliphatic linker having one carbon replaced by S.

35. A compound as claimed by any one of Claims 1 through 34 wherein the aliphatic linker is substituted with from one to three substituents each independently selected from R30.

36. A compound as claimed by Claim 35 wherein the aliphatic linker is substituted with from one to two substituents each independently selected from R30.

37. A compound as claimed by any one of Claims 1 through 36 wherein each R30 is independently selected from the group consisting of C1-C6 alkyl.

38. A compound as claimed by any one of Claims 1 through 37 wherein each R30 is independently selected from the group consisting of C2-C3 alkyl.

39. A compound as claimed by any one of Claims 1 through 36 wherein R30 is independently selected from the group consisting of aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C3-C6 cycloalkylaryl-C₀₋₂-alkyl.

40. A compound as claimed by Claim 39 wherein Y is O and E is -CH₂COOH.

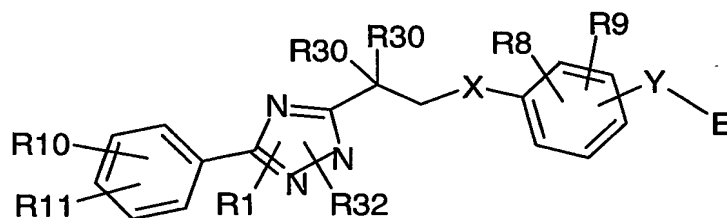
- 151 -

41. A compound as claimed by any one of Claims 1 through 40 wherein U is substituted with methyl.

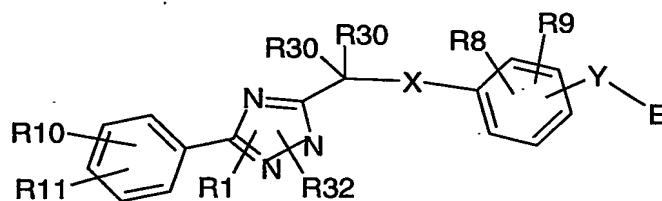
42. A compound as claimed by any one of Claims 1 through 41 wherein U is
5 methylene.

43. A compound as claimed by any one of Claims 1 through 16 and 22
through 42 wherein R10 and R11 combine to form a fused 6 membered ring.

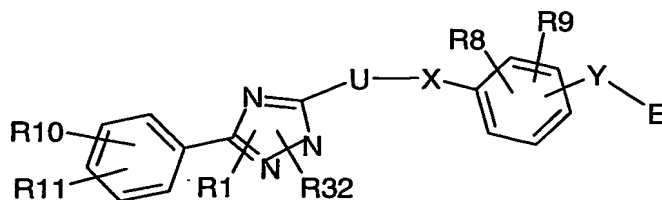
10 44. A compound as claimed by any one of Claims 1-3, 8-13, 15-24, 26, and
36-41 represented by the following Structural Formula IV:



15 45. A compound as claimed by any one of Claims 1-3, 8-13, 15-24, 26, 36-41
represented by the following Structural Formula V:

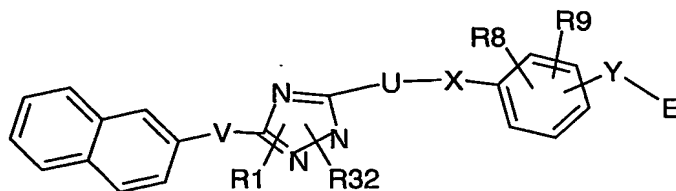


46. A compound as claimed by any one of Claims 1-3, 8-13, 15-24, 26, 36-41,
represented by the following Structural Formula VI:

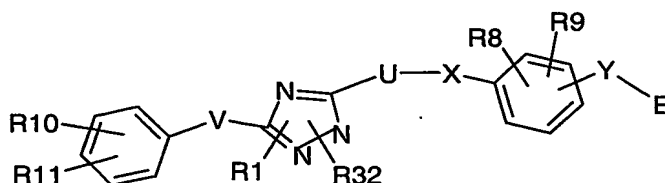


- 152 -

47. A compound as claimed by any one of Claims 1-3, 8-13, 15-24, 26, 36-41, represented by the following Structural Formula VIII:



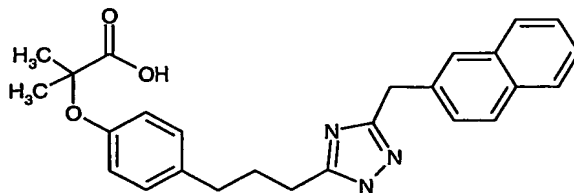
48. A compound as claimed by any one of Claims 1-3, 8-13, 15-24, 26, 36-41, represented by the following Structural Formula IX:



49. A compound as claimed by any one of Claims 1 through 48 wherein X and Y are substituted at a 1,4-position, such that X and Y are para substituted to one another.

50. A compound as claimed by any one of Claims 1 through 48 wherein X and Y are substituted at a 1,3-position, such that X and Y are meta substituted to one another.

51. A compound as claimed by any one of Claims 1 wherein the compound is a compound of the formula:



or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

52. A compound as claimed by any one of Claims 1 through 50 wherein X is a bond.

- 153 -

53. A compound as claimed by any one of Claim 1 which is 2-Methyl-2-{4-[3-(5-naphthalen-2-ylmethyl-2H-[1,2,4]triazol-3-yl)-phenoxy]proprionic acid.

5 54. A compound as claimed by any one of Claims 1 through 53 that is the S conformation.

55. A compound as claimed by any one of Claims 1 through 53 that is the R conformation.

10 56. A pharmaceutical composition, comprising as an active ingredient, at least one compound as claimed by any one of Claims 1 through 55 together with a pharmaceutically acceptable carrier or diluent.

15 57. A method of modulating a peroxisome proliferator activated receptor, comprising the step of contacting the receptor with at least one compound as claimed by any one of Claims 1 through 55.

20 58. A method for treating diabetes mellitus in a mammal, comprising the step of administering to the mammal in need thereof a therapeutically effective amount of at least one compound of Claims 1 through 55.

25 59. A method for treating metabolic disorder in a mammal, comprising the step of administering to the mammal in need thereof a therapeutically effective amount of at least one compound of Claims 1 through 55.

60. A method of Claim 59 wherein the mammal in need thereof is diagnosed as suffering from metabolic disorder.

30 61. A method for selectively modulating a PPAR delta receptor comprising administering a compound as claimed by any one of Claims 1 through 55 to a mammal in need thereof.

- 154 -

62. The manufacture of a medicament for use in the treatment and/or prevention of a metabolic disorder, wherein the compound is a compound as claimed by any one of Claims 1 through 55.

5 63. A method for treating atherosclerosis in a mammal, comprising the step of administering to the mammal in need thereof, a therapeutically effective amount of at least one compound of Claims 1 through 55.

10 64. A compound as Claimed by any one of Claims 1 through 55 for use as a pharmaceutical.

15 65. A method for treating or preventing the progression of cardiovascular disease in a mammal in need thereof comprising administering a therapeutically effective amount of at least one compound as Claimed by any one of Claims 1 through 55.

66. A method as claimed by Claim 65 wherein the mammal is diagnosed as being in need of such treatment.

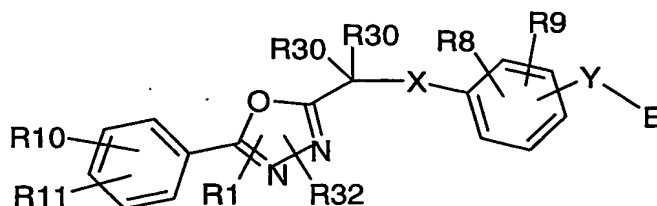
20 67. A compound as claimed by any one of Claims 1 through 55 wherein the compound is radiolabeled.

68. A compound as disclosed by any one of the Examples herein.

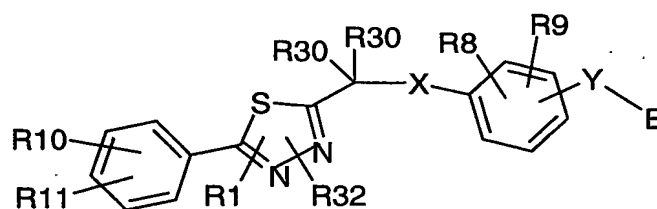
25 69. All methods disclosed herein of preparing the compounds represented by Structural Formula I.

70. A compound as claimed by any one of claims 1, 4, 5, 6, 9-13, 15-24, 26, or 36-41 represented by the structural formula X:

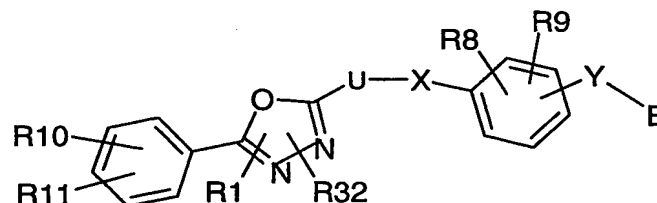
- 155 -



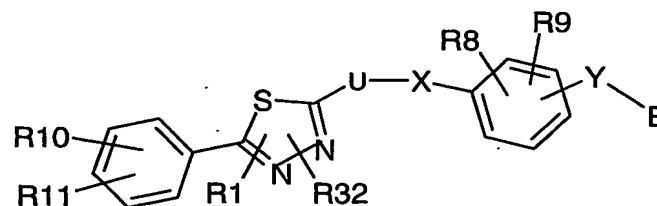
71. A compound as claimed by any one of claims 1, 5, 7, 9-13, 15-24, 26, 36-41 represented by the structural formula XI:



72. A compound as claimed by any one of claims 1, 4, 5, 6, 9-13, 15-24, 26, or 36-41 represented by the structural formula XII:

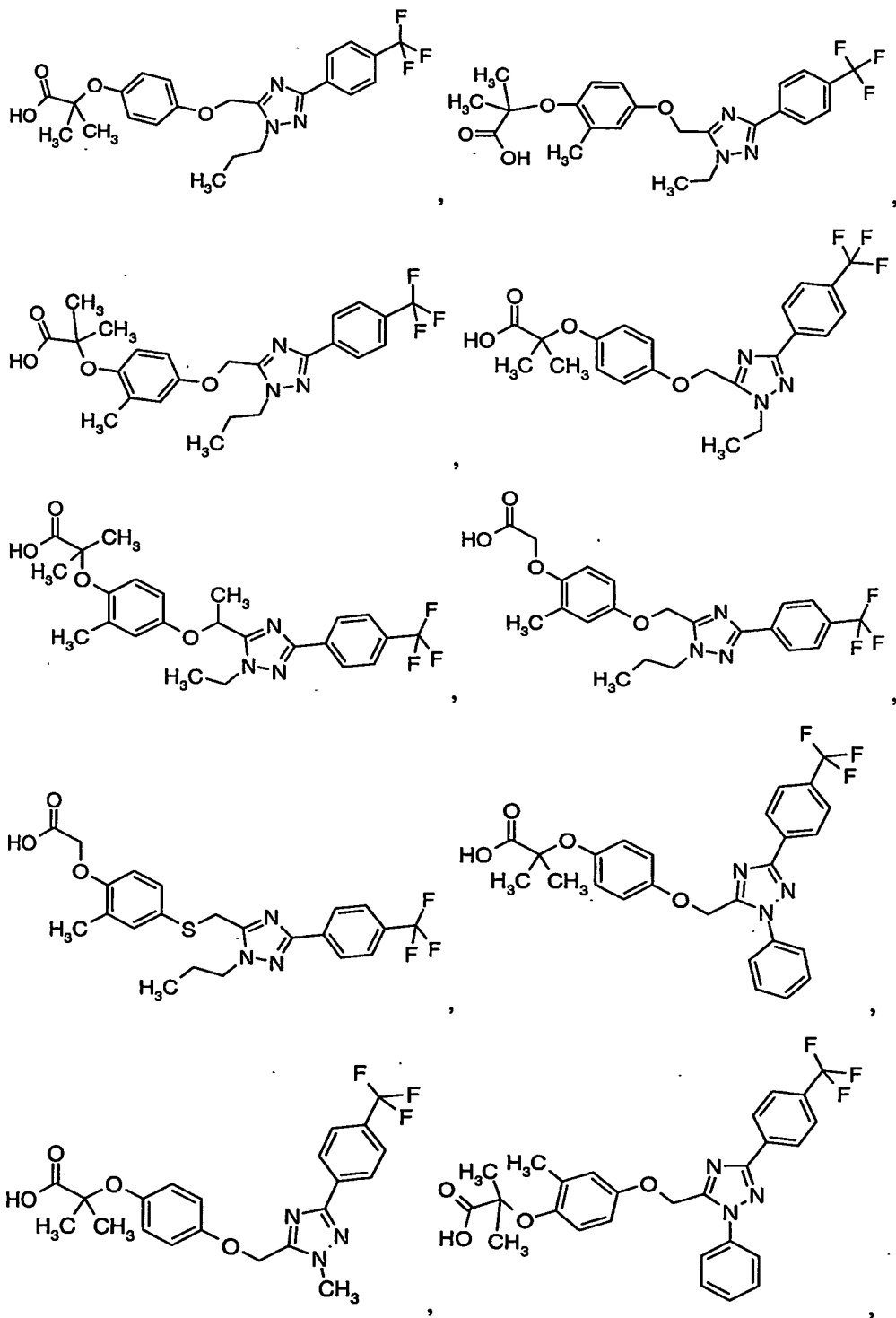


73. A compound as claimed by any one of claims 1, 5, 7, 9-13, 15-24, 26, 36-41 represented by the structural formula of formula XIII:

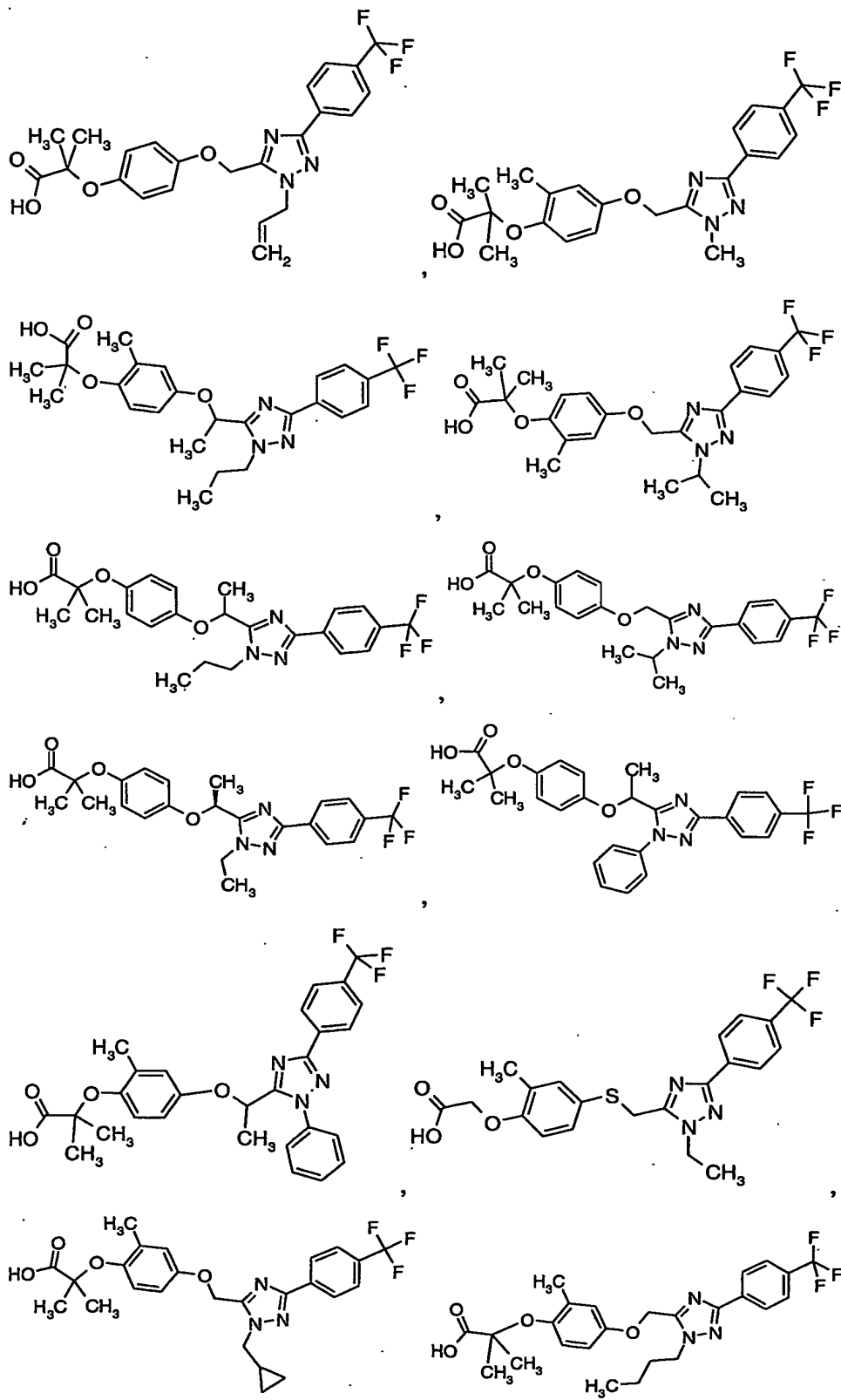


74. A compound as claimed by Claim 45 wherein the compound is selected from the group consisting of:

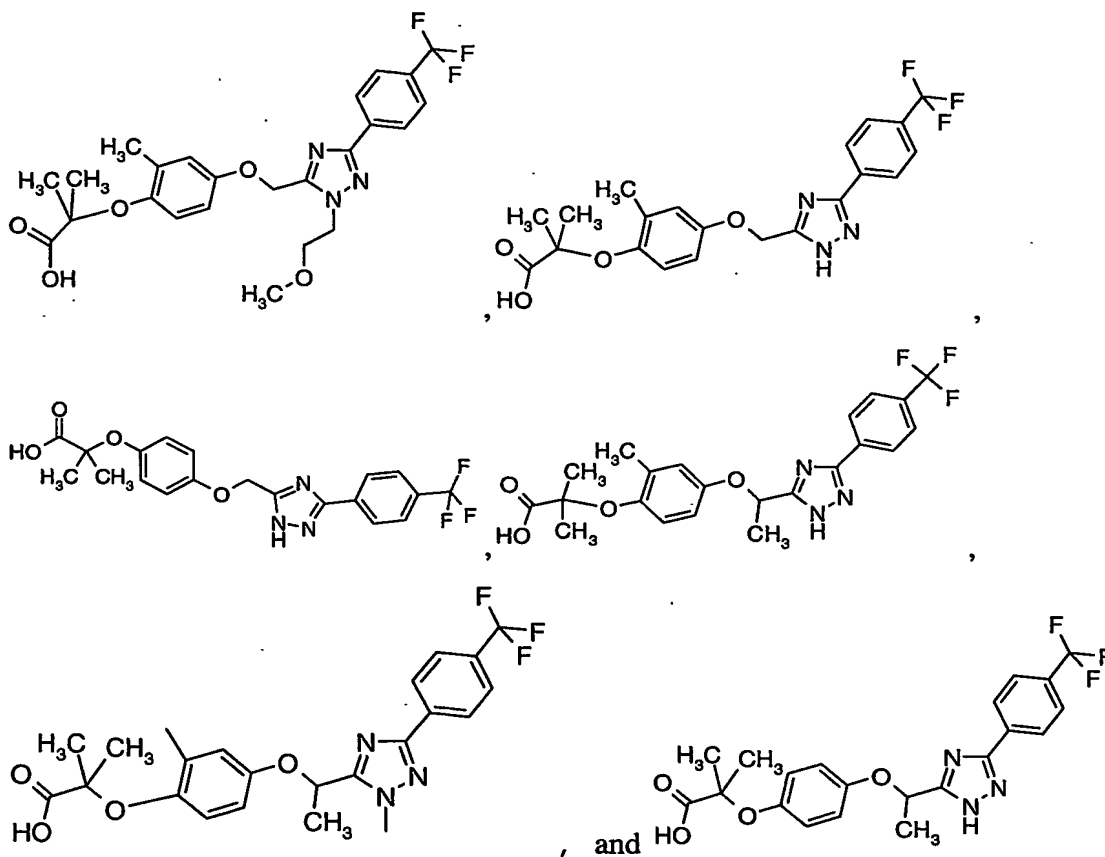
- 156 -



- 157 -



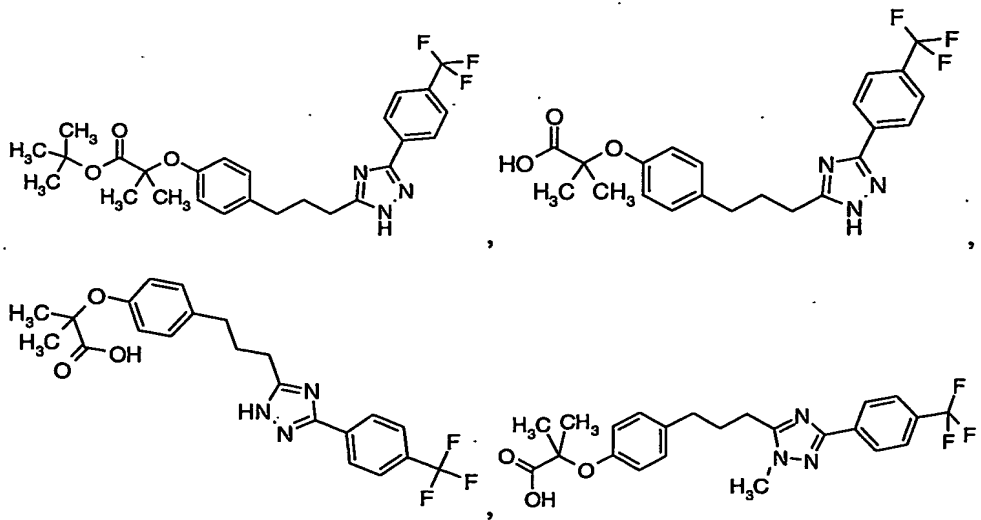
- 158 -



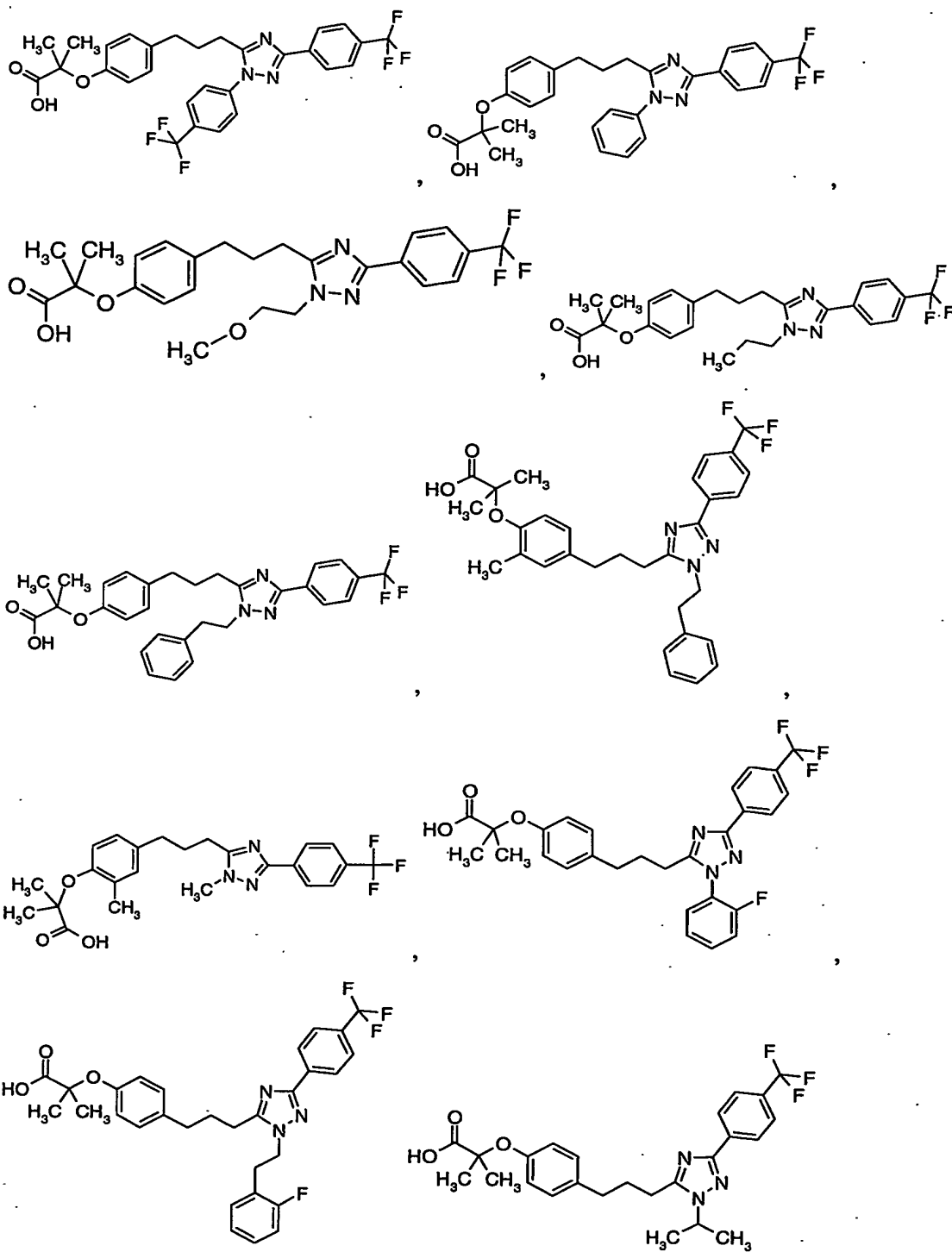
or a pharmaceutically salt, solvate, or hydrate thereof.

5

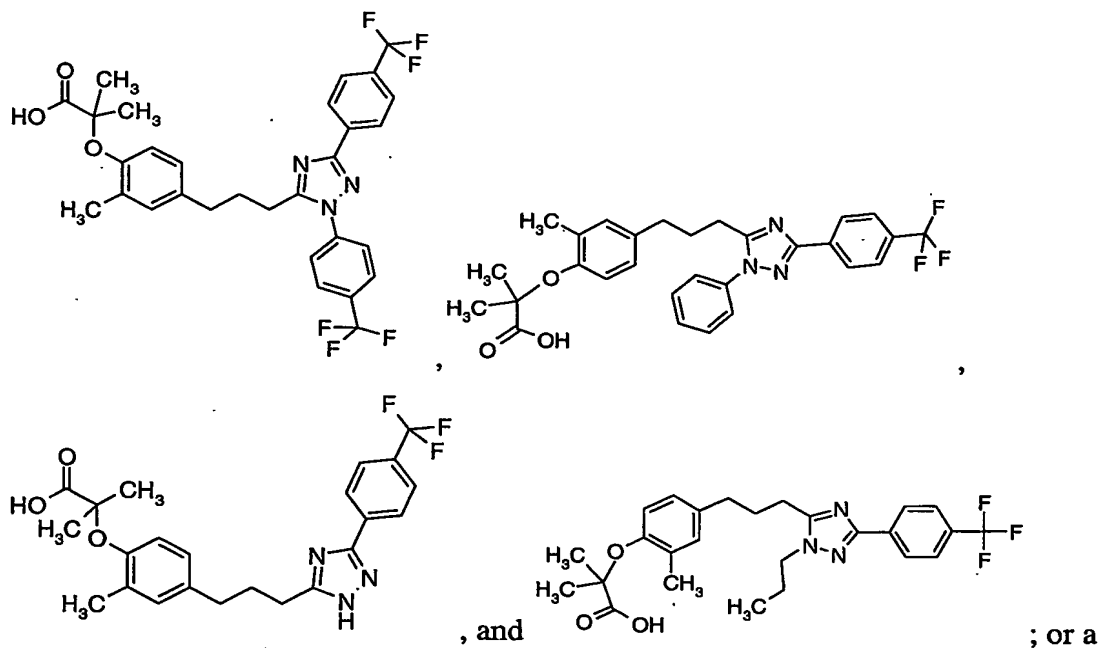
75. A compound as claimed by Claim 46 wherein the compound is selected from the group consisting of:



- 159 -

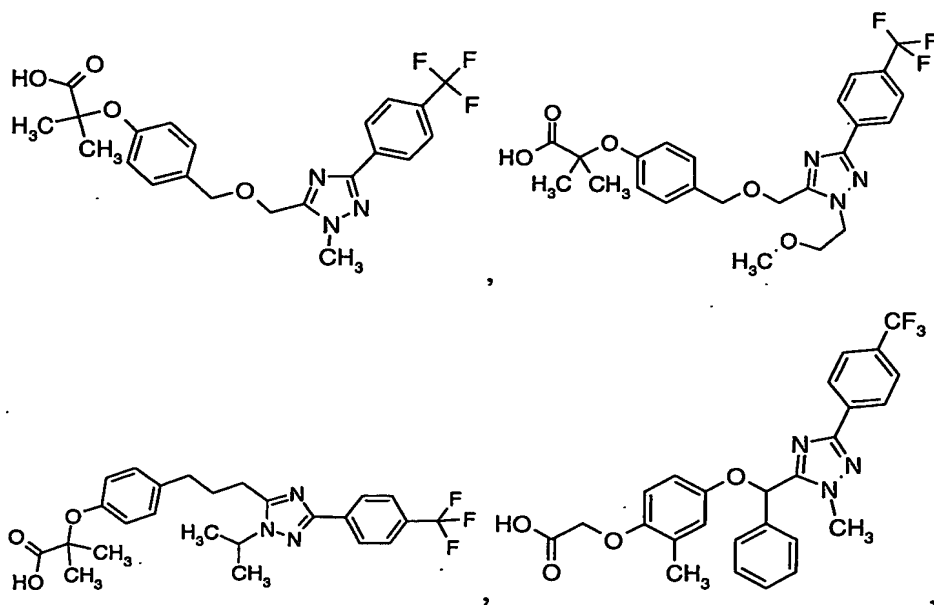


- 160 -

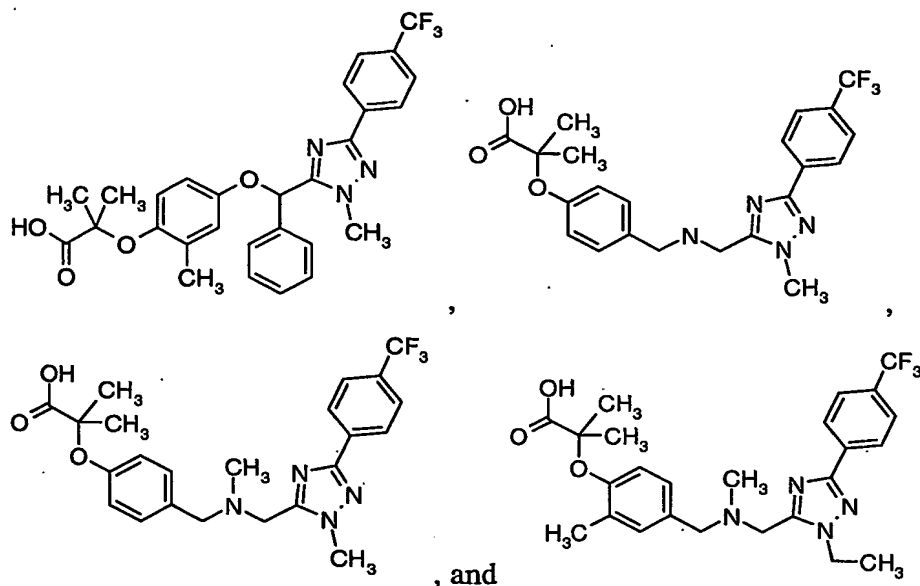


pharmaceutically acceptable salt, solvate, or hydrate thereof.

76. A compound as claimed by Claim 46 wherein the compound is selected
 5 from the group consisting of:

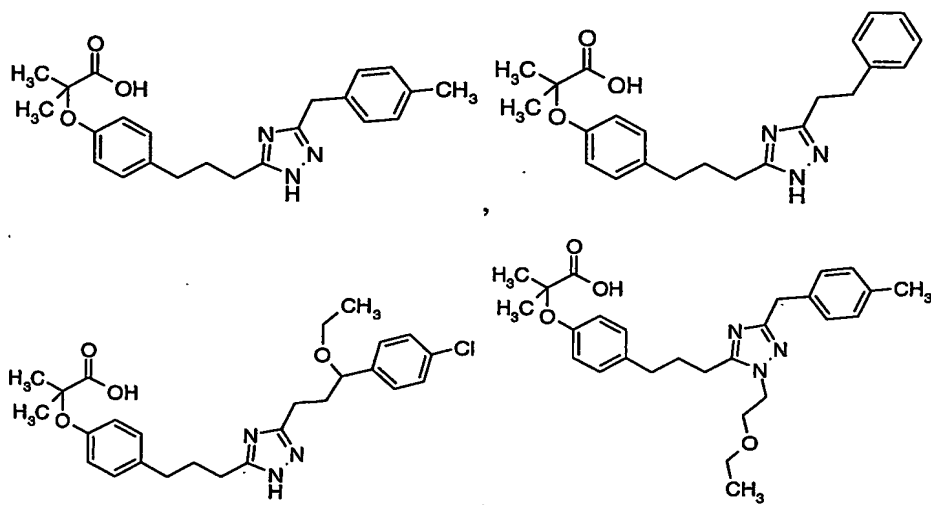


- 161 -

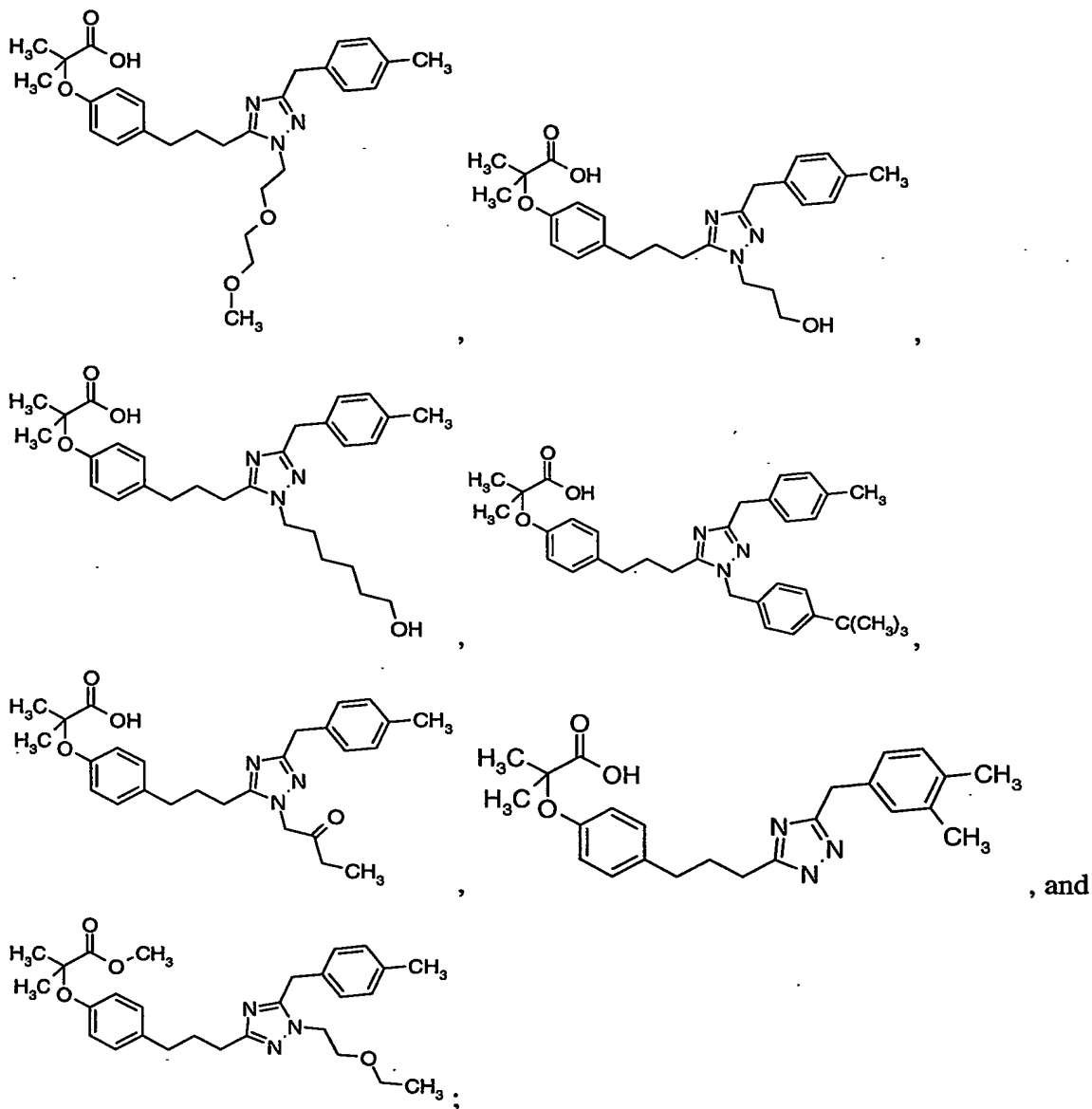


or a pharmaceutically salt, solvate, or hydrate thereof.

- 5 77. A compound as claimed by Claim 48 wherein the compound is selected from the group consisting of:



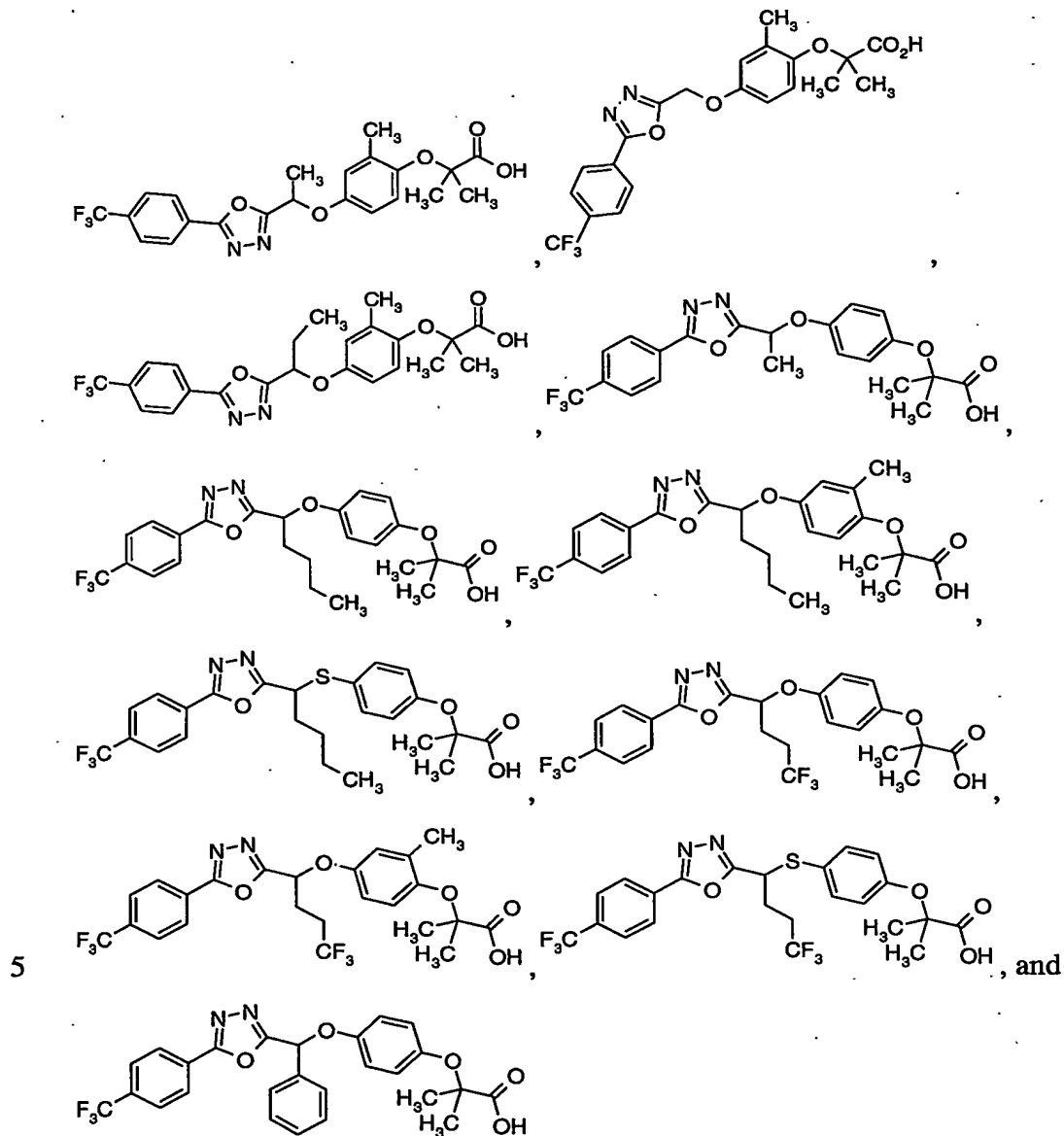
- 162 -



5 or a pharmaceutically salt, solvate, or hydrate thereof.

78. A compound as claimed by Claim 70 wherein the compound is selected from the group consisting of:

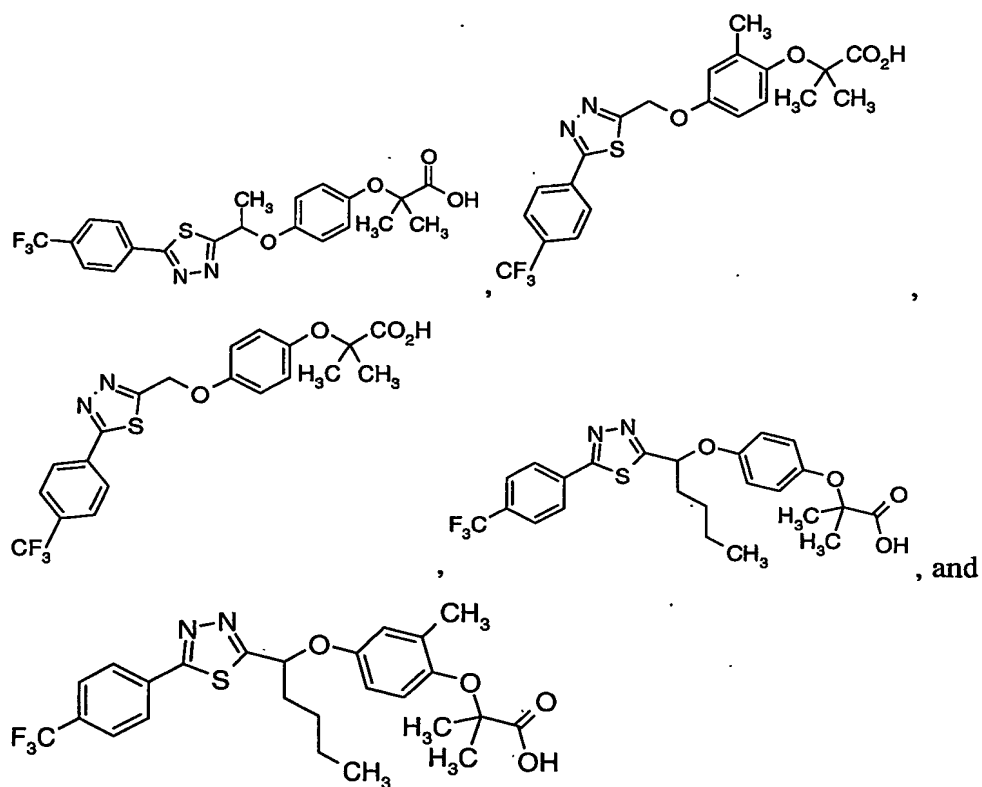
- 163 -



or a pharmaceutically salt, solvate, or hydrate thereof.

79. A compound as claimed by Claim 71 wherein the compound is selected
 10 from the group consisting of:

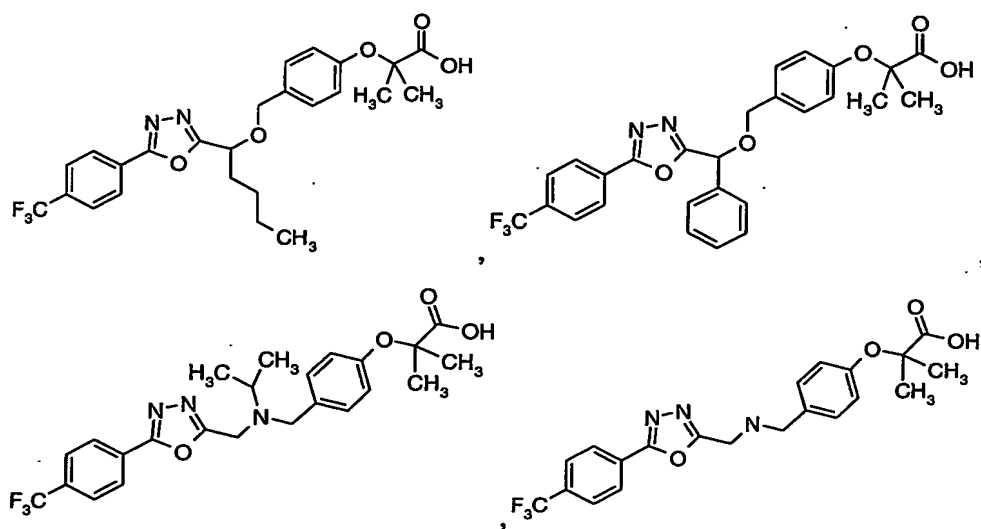
- 164 -



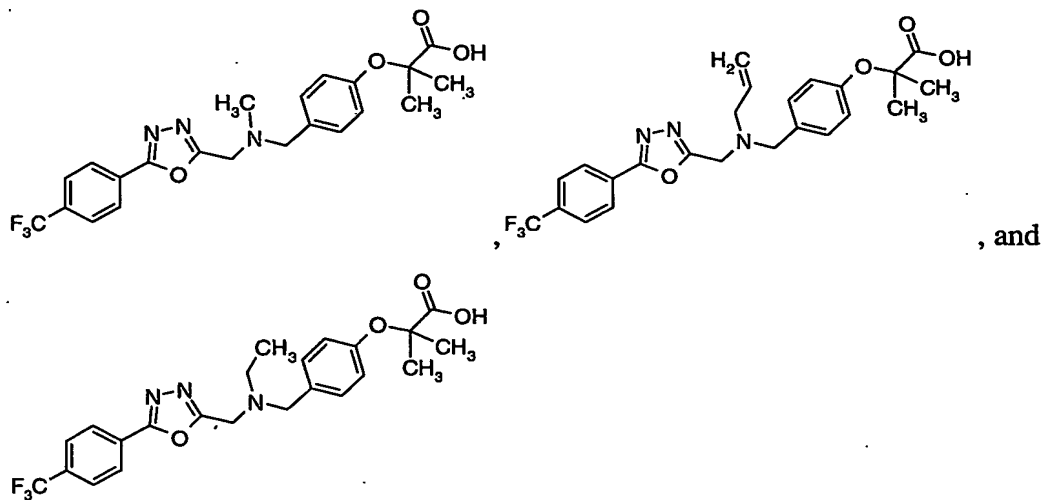
or a pharmaceutically salt, solvate, or hydrate thereof.

5

80. A compound as claimed by Claim 72 wherein the compound is selected from the group consisting of:

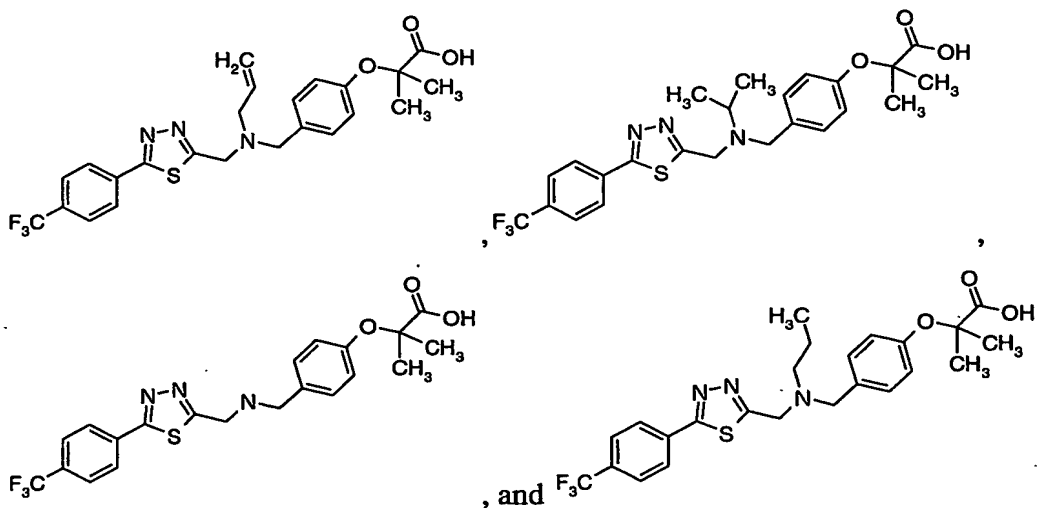


- 165 -



or a pharmaceutically salt, solvate, or hydrate thereof.

- 5 81. A compound as claimed by Claim 73 wherein the compound is selected from the group consisting of:



or a pharmaceutically salt, solvate, or hydrate thereof.

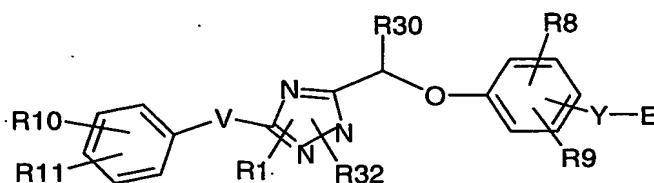
10

82. A pharmaceutical formulation comprising a compound as claimed by any one of Claims 1 through 55, Claims 70 through 81, 83 or 84 and at least one pharmaceutically acceptable excipient or carrier.

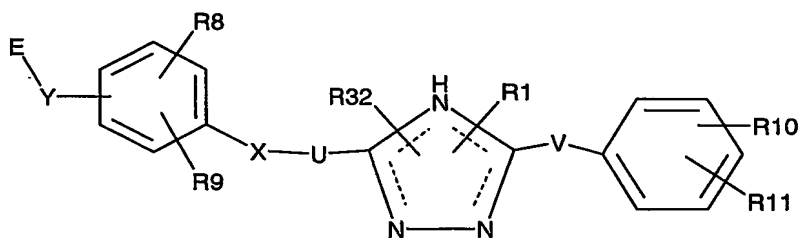
15

83. A compound as claimed by any one of Claims 1, 2, 3, 8, 12-26, 39, 40, and 43 of the structural formula:

- 166 -



84. A compound as claimed by any one of claims 1, of the Formula Ia:



Ia

and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

- (a) R1 is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, C₁-C₈ heteroalkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and, wherein C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents independently selected from R1';
- (b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR₁₂, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀₋₄-alkyl, heteroaryl, heterocycloalkyl, C(O)R₁₃, COOR₁₄, OC(O)R₁₅, OS(O)₂R₁₆, N(R₁₇)₂, NR₁₈C(O)R₁₉, NR₂₀SO₂R₂₁, SR₂₂, S(O)R₂₃, S(O)₂R₂₄, and S(O)₂N(R₂₅)₂; R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄ and R₂₅ are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;

- 167 -

- (c) V is selected from the group consisting of C₀-C₈ alkyl and C₁₋₄-heteroalkyl;
- (d) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;
- 5 (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is substituted with from one to four substituents each independently selected from R₃₀;
- (f) Y is selected from the group consisting of C, O, S, NH, and a single bond;
- 10 (g) E is C(R₃)(R₄)A or A and wherein
- (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkynitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R⁷;
- 15 (ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;
- (iii) R₃ is selected from the group consisting of hydrogen, C₁-C₅ alkyl, and C₁-C₅ alkoxy; and
- 20 (iv) R₄ is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R₃ and R₄ are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R₂₆;
- 25 (h) R₈ is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;
- (i) R₉ is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR₂₉, and
- 30 wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with

- 168 -

from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C₁-C₄ alkyl;

- (j) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkylenyl, C₁-C₆ alkyl-COOR12'', C₀-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', OS(O)₂R16', N(R17')₂, NR18'C(O)R19', NR20'SO₂R21', SR22', S(O)R23', S(O)₂R24', and S(O)₂N(R25')₂; and wherein aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three independently selected from R28; and wherein R10 and R11 optionally combine to form a 5 to 6 membered fused bicyclic ring with the phenyl to which they are bound;
- (k) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (l) R30 is selected from the group consisting of C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and wherein C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;
- (m) R32 is selected from the group consisting of a bond, hydrogen, halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, and C₁-C₆ alkyloxo; and
- (n) ---- is optionally a bond to form a double bond at the indicated position.